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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,885	03/22/2004	John W. Benbow	PC25078A	2214

28523 7590 04/24/2006
PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER

TUCKER, ZACHARY C

ART UNIT PAPER NUMBER

1624

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/805,885

Applicant(s)

BENBOW ET AL.

Examiner

Zachary C. Tucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 5-14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Requirement for Restriction

A Requirement for Restriction in this application was mailed 23 February 2006. Applicant's election of the invention of Group I, claims 1-4, in the reply filed on 21 March 2006, is acknowledged.

Claims 5-14 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions.

In the Requirement for Restriction letter, a further requirement was set forth, for applicants to elect a single disclosed species of formula (I) in claim 1, regardless of which Group is elected. In response to this requirement, the compound 8-fluoro-4-cyclohexylamino-2H-[1,2,4]triazolo[4,3-a]quinoxaline-1-one, which is the third compound claimed in claim 4 of this application. Claims 1-4 all read on this species.

A search of instant claim 1, based on the elected species, wherein one of R^a and R^b is a saturated carbocyclic group, was performed, and no prior art anticipating or rendering obvious the elected species was found, whereupon the search was broadened, to include *all* of instant claims 1-4.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I) and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for prodrugs of

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formula (I) compounds and the salts of those prodrugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making the determination of whether or not a claimed invention is supported by a given disclosure to sufficient to enable a person of ordinary skill in the art to which it pertains, to make and/or use the invention, given said disclosure, the Office relies upon factors promulgated in the decision rendered in *In re Wands*:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each factor will be addressed, first with respect to the non-enabled solvates, and then with respect to the non-enabled prodrugs.

(A) Though it might appear that the prodrugs embodiment of instant claim 1, from which claims 2-4 depend, is limited only to compounds of formula (I) embraced by the structure diagram depicted, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

“is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug.” Thus, an important requirement of prodrugs of compounds of formula (I) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only those that undergo some sort of enzymatic solvolysis, which are commonly cited as examples. A prodrug may be a Mannich base

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(imine), an acyclic precursor to a heterocyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug is not necessarily even structurally related to the compound of which it functions as a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a compound of formula (I) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman, cited in the specification at page 15, teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug is desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art insofar as the prodrug embodiment of instant claims 1-4 is concerned is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the

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other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically derived when the compound in question is a novel compound, as are compounds of formula (I). It cannot be predicted which compounds will serve as prodrugs for formula (I) compounds.

(F) No specific guidance relevant to the preparation of prodrugs of formula (I) compounds is provided in the specification.

No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than acylated derivatives.

(G) No working examples, out of the 127 preparative examples, of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of compounds of formula (I), a complete structure activity analysis of all of the

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compounds falling within formula (I) would have to be completed. This analysis would involve thousands upon thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of these inactive compounds would have to be completed, and compounds that are converted to active compounds of formula (I) *in vivo* identified. This research would potentially be inconclusive and could take years. A major part of the work necessary for realizing the full scope of prodrugs of formula (I) compounds would be that pertaining to totally new compounds not bearing any structural similarity to the compounds of formula (I), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the compounds of formula (I) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics (drugs, in other words) are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a certain prodrug of a formula (I) compound were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations."

Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making

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prodrugs of compounds of formula (I), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of the term “prodrug thereof,” in reference to formula (I) in claim 1, or the salts of the prodrug, also specified in claim 1, cannot be determined by one of ordinary skill in the art.

Applicants may opine that one of ordinary skill understands what the term “prodrug” means. The examiner is not pretending that one of ordinary skill does not understand what *function* a prodrug serves. This is not the issue here. What is claimed is chemical compounds which serve as a prodrug for the compounds of formula (I). The claim, therefore, is drawn to a group of *molecular structures*, that when subjected to a biological milieu in a live animal, will be metabolically converted to a compound of formula (I). One of ordinary skill cannot possibly be aware of the full scope of all of the different molecular arrangements which will provide the compounds (I) upon being metabolized, in all animals. Page 7, lines 9-15, of the specification only provides an extremely general description of what constitutes a prodrug. No particular type of prodrug is discussed in this passage.

As evidenced by the Al-Dabbagh and Smith reference, cited *supra*, in the rejection of the claimed prodrugs under the first paragraph of 35 U.S.C. 112, animals will differ significantly in the manner that xenobiotics are metabolized. Therefore, a compound that is a prodrug in humans is not necessarily a prodrug in a cat, for example. So, which compounds will act as prodrugs for a certain formula (I) compound will not necessarily be the same in different animal species. Arguably, therefore, the identity of the prodrugs according to instant claim 1 will differ based on the animal to which the prodrug is to be administered. Since no animal species is recited in instant claim 1, with respect to the prodrugs, the identity of the prodrugs is dependent on an undefined variable.

Claim 4, in addition to being indefinite because it depends from an indefinite base claim, is further indefinite because claim 1, from which claim 4 depends, does not provide antecedent basis for the fourth named compound of claim 4, 8-fluoro-4-isopropyl-2H-[1,2,4]triazolo[4,3-a]quinoxaline-1-one. The proviso in claim 1 excludes from formula (I) those compounds wherein one of R^a and R^b is hydrogen or isopropyl and R¹ is fluoro-. In fact, this excluded compound (fourth named compound in instant claim 4) is disclosed in Table IV, on page 2247, of the Sarges et al reference, which is relied upon in the rejection under 35 U.S.C. 103(a) of claims 1-4 in this Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarges et al, *Journal of Medicinal Chemistry*, vol. 33(8), pages 2240-2254 (1990).

At the time the invention was made, compounds according to claims 1-4 would have been obvious to one of ordinary skill in the art, given the teaching of Sarges et al.

Sarges et al reports a series of 4-amino- [1,2,4]triazolo[4,3-a]quinoxaline compounds having antagonist activity at the adenosine (A₁) receptor. In Table IV on page 2247 of the article, two compounds embraced by formula (I) are disclosed, designated numbers 137 and 138. These compounds correspond to formula (I) where R² is hydrogen; R¹ is fluoro; R^a is hydrogen or isopropyl; R^b is hydrogen. The "X" group in these compounds, wherein "X" corresponds to the structural variable "X" in the structure diagram shown at the top of Table IV on page 2247, is OH. This OH group corresponds to the carbonyl group on the triazolo ring in compounds according to instant claim 1. The carbonyl shown in formula (I) is simply a tautomeric form of the hydroxyl shown in the Sarges et al reference. Sarges et al's compounds exist as keto-enol tautomers with the corresponding carbonyl form at the "X" position. Compounds 137 and 138 of Sarges et al are excluded by the language of instant claim 1, however, in the proviso in the latter part of the claim.

The Sarges et al article is a detailed structure activity study on the aforementioned triazoloquinoxaline adenosine receptor antagonists. At page 2243, the reference teaches that the most potent adenosine receptor antagonists were those with halogen on the benzo- ring, particularly those bearing a chlorine substitution at the 8-position, which corresponds to R¹ of formula (I) of instant claim 1. In light of this simple

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suggestion, one of ordinary skill in the art, motivated by a desire to make more potent adenosine receptor antagonists, would replace the 8-fluoro substituent on compounds 137 and 138 with chlorine.

Were the fluorine atom of compound 138 replaced with chlorine, the second named species in instant claim 4, 8-chloro-4-(isopropylamino)-2*H*-[1,2,4]triazolo[4,3-*a*]quinoxaline-1-one, results. This compound is therefore obvious over the Sarges et al reference's disclosure of the corresponding 8-fluoro compound and the accompanying teaching that the most potent activities are observed in compounds bearing an 8-chloro substitution.

Compounds 137 and 138 of Sarges et al, modified by replacing the fluorine atom with a chlorine atom, are embraced by instant claims 1-4 wherein R^a is hydrogen or isopropyl; R^b is hydrogen; R¹ is chloro; R² is hydrogen.

Allowable Subject Matter

Compounds according to instant claim 4, save for the second and fourth named compounds are novel and unobvious in view of the prior art.

Upon amendment of the claims so as to overcome the rejections set forth herein, claims 5-9 will be eligible for rejoinder.

Upon rejoinder, methods according to claims 6-9 will be rejected under the first paragraph of 35 U.S.C. 112, for lack of a disclosure enabling the practice of said methods. Glycogen synthase kinase inhibitors, at the time the invention was made, were not developed to the point of being readily understood by and applied in clinical practice by the physician of ordinary skill. A claim drawn generally to inhibition of glycogen synthase kinase-3 activity in a mammal in need of such inhibition, such as

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instant claim 9, is both indefinite and not enabled. Which mammals need GSK-3 inhibition and which do not is not known by those of ordinary skill. It is also not known whether a mammal in good health could benefit from GSK-3 inhibition and if said mammal therefore needs GSK-3 inhibition. Claim 9 is not enabled because the "how to use" portion of 35 U.S.C. 112, first paragraph, is not fully satisfied. The utility of GSK-3 inhibition, generally, is not fully described. As such, instant claim 9 reads on treatment of substantially all diseases.

As a courtesy to applicants, the examiner submits herewith some references which most likely will be relied upon in making the determination of non-enablement of the methods:

Eldar-Finkelman and Ilouz "Challenges and opportunities with glycogen synthase kinase-3 inhibitors for insulin resistance and Type 2 diabetes treatment" Expert Opinion on Investigational Drugs, vol. 12(9), pages 1511-1519 (2003).

Martinez et al, "Glycogen Synthase Kinase 3 (GSK-3) Inhibitors as New Promising Drugs for Diabetes, Neurodegeneration, Cancer, and Inflammation" Medical Research Reviews, vol. 22(4), pages 373-384 (2002).

Martinez et al teaches that GSK-3 inhibitors may prove useful in the treatment of several disease states, including cancers, "inflammatory diseases" and neurodegenerative diseases. The conclusion statement at the end of the Martinez et al article states flatly that the clinical utility of GSK-3 inhibitors awaits animal and human trials.

Eldar-Finkelman and Ilouz teaches that GSK-3 inhibitors may provide a therapeutic alternative to insulin and/or treatment of Type 2 diabetes and obesity (page 1516, under the heading "Expert Opinion." The benefits of these drugs in clinical application "are yet to be evaluated" (page 1516, bottom of column two) is the last statement in the article.

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Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

A handwritten signature in black ink, appearing to read 'Zachary Tucker', with a long horizontal line extending to the right.